Chapter 4

Adhesive Materials for Biomedical Applications

Andrea J Vernengo

Additional information is available at the end of the chapter

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Abstract

Recently, polymeric bioadhesives have become known as promising alternatives to sutures, staples, and wires. Traditional wound closure techniques are time-consuming to apply and cause additional tissue damage. In instances of large-scale hemorrhage or minimally invasive laparoscopic surgery, sutures are impractical to apply. Alternatively, newly developed bioadhesives are polymers that can be dripped or sprayed over superficial or internal injuries, solidifying in situ to form a seal that apposes tissue or arrests bleeding over large areas. This review will outline the main categories of polymers that have been investigated for these applications. The chemistry, mechanisms of adhesion, and advantages and limitations of each category will be described. In addition, needs for next-generation adhesives in tissue engineering will be discussed. For the repair of certain load-bearing areas of the body, such as cartilage and the intervertebral disc, scaffold adhesion is necessary for anchoring the scaffold in place and providing adequate transmission of forces. Researchers continue developing new formulations that exhibit improved biocompatibility, strength, elasticity, and degradability. These advances promise to improve clinical outcomes by enhancing bleeding control and wound healing. In the long term, bioadhesives will play an important role in making orthopedic and musculoskeletal tissue engineering clinically feasible.

Keywords: surgical sealants, glues, bioadhesives, tissue adhesion, in situ forming hydrogels, tissue engineering

1. Introduction

Sutures, wires, and staples are routine ways for achieving closure of superficial or internal tissues, yet there are several limitations to these traditional closure methods. For instance, the application of sutures is time-consuming and requires the penetration of surrounding tissues, causing additional damage [1] and increasing potential for infection [2]. The suture points also

cause high stress concentration [3], which can result in more pain for the patient. Gaps in the injury site left behind due to incomplete suturing can cause leakage, and depending on the type of fluid (bowel content, bile, or cerebral spinal fluid), serious clinical complications could result [4, 5]. Finally, there are surgical situations where sutures, staples, and wires are difficult, if not impossible, to implement, such as in minimally invasive laparoscopic surgery [2, 6], or when trauma results in large-scale incompressible hemorrhage [7].

Over the past few decades, a variety of new flexible polymers with bioadhesive properties have emerged, which offer alternatives to traditional closure methods. These polymers have the ability to fill irregularly shaped cavities or be spread over large areas of tissue to quickly form a seal that mitigates bleeding. Commonly, the monomer or macromer components are applied as liquids and solidify on the tissue via in situ polymerization or cross-linking reaction. Polymeric bioadhesives have been studied for approximating tissues in surface wounds (glues), controlling bleeding (hemostats), and closing of fluid or air leaks (sealants) [8]. This review will outline the main classes of bioadhesives that have been studied for these applications, both in the clinic and in scientific literature, including cyanoacrylates, proteins, hydrogels, polysaccharides, and nature-inspired synthetic polymers. An emphasis is placed on polymer chemistry, mechanisms of adhesion, and the advantages and disadvantages of each material class. Because it is impossible to compare quantitative data generated by various researchers in separate experiments [1], the descriptions will emphasize qualitative findings. The final component of this review focuses on emerging applications for bioadhesives in regenerative medicine and the unmet needs that still exist.

2. Main classes of adhesives

2.1. Cyanoacrylates

Cyanoacrylate tissue adhesives are monomers that polymerize in the presence of aqueous milieu to create a solid layer that joins apposed wound edges [9]. The liquid monomers have a high reactivity; thus, polymerization happens in seconds without addition of a catalyst or elevated temperature [1]. When the monomers are applied on tissue, the liquid flows into the existing crevices, sealing by a mechanical interlock upon curing [1]. The NH_3 groups in tissue also participate in the polymerization, contributing toward the strong bonding that cyanoacrylates form [10].

Cyanoacrylates have been successfully applied in a clinical setting. Dermabond®, composed of. 2-octyl-cyanoacrylate (**Figure 1A**), was approved by the FDA in 1998 for the closure of topical skin incisions. The polymer degrades in 7–10 days [1]. Dermabond was compared to the use of metal clips in the closure of wounds from thyroidectomy in 70 patients [11]. In terms of quality of skin closure and cosmetic outcomes, both closure methods yielded similar results. However, according to patient input, postoperative management was easier in the Dermabond group. Poly(2-octyl-cyanoacrylate) has also been reported to have antimicrobial properties for 72 h after it is first applied. The cured material, applied on superficial wounds, was an effective

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barrier against infection when used with best approximation of wound lips after plastic surgery [12].

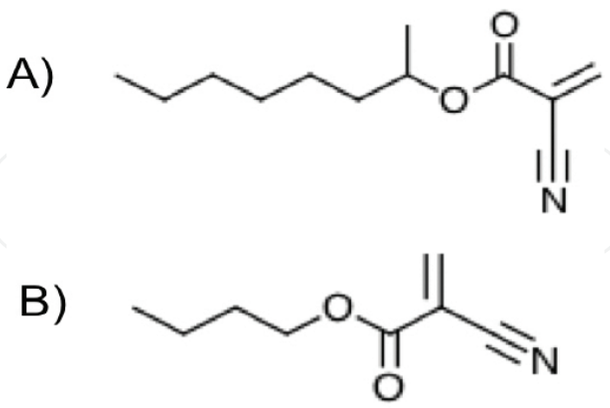

Figure 1. The structures of the cyanoacrylate tissue adhesives (A) 2-octyl-cyanoacrylate and (B) N-butyl-2-cyanoacrylate.

Another clinical study was conducted on 35 patients with inguinal hernias that were repaired with a prosthesis fixed with n-hexyl-α-cyanoacrylate. Results were compared with fixation with sutures. The use of cyanoacrylate adhesive instead of sutures did not alter the relapse rate, but it did significantly reduce surgical time and postoperative pain with no complications [13]. N-hexyl-α-cyanoacrylate was also used successfully in a rat model of microvascular anastomosis. In the experimental technique being evaluated, the thermoreversible polymer Polaxomer® 407 was injected into both ends of severed blood vessel. The ends were then approximated, and the glue was applied circumferentially. The method was reported as easy to apply, faster than sutures, and produced a lower foreign body response [14]. Idle et al. [15] reported successful use of N-butyl-2-cyanoacrylate (**Figure 1B**) as a hemostatic agent to prevent hemorrhage after tooth extraction. At 2 months, the glue was completely resorbed and the tooth socket healed.

There are some drawbacks to cyanoacrylate adhesives that limit the use to external, temporary applications. For instance, the mechanical properties of cyanoacrylate adhesives have been reported to be weaker than sutures [16]. In addition, the cured sealant is brittle, and thus, researchers have sought to modify the polymer structure to enhance flexibility. Poly(L-lactide-co-ε-caprolactone (PLCL) is a synthetic copolymer that was used as an additive in ethyl-2-cyanoacrylate (EC) and allyl-2-cyanoacrylate (AC) monomers. All formulations containing PLCL resisted breaking when subjected to 30 cycles of bending stress. In contrast, EC and AC broke after one and seven cycles, respectively [17].

There are also concerns over potential cytotoxicity and inflammatory responses associated with the use of cyanoacrylate adhesives. Degradation of cyanoacrylates occurs via hydrolysis. The by-products, cyanoacetate and formaldehyde, can potentially cause toxicity [18–20]. The first cyanoacrylate adhesives applied for medical purposes were ethyl-2-cyanoacrylate (**Figure 2A**) and methyl-2-cyanoacrylate (**Figure 2B**). These short-chain monomers exhibited fast

degradation upon polymerization, allowing for the accumulation of higher amounts of formaldehyde and/or cyanoacetate in the tissue. These monomers have been abandoned [1] and replaced with those with longer alkyl chains, like n-hexyl-α-cyanoacrylate, N-butyl-2-cyanoacrylate, and 2-octyl-cyanoacrylate, although concerns over the use of these formulations exist as well. The biocompatibility of Glubran 2®, an n-butyl cyanoacrylate-based adhesive, was evaluated. Extracts of cured glue were applied over a monolayer of L929 fibroblast cells. Severe cytotoxicity was observed with the undiluted extracts, which disappeared when the extracts were diluted 1:10 [21]. In a clinical report, a foreign body response was observed 3 weeks after using of Dermabond to seal a superficial wound on the wrist of a 39-year-old [22]. The authors recommend informing patients of the potential risk of an inflammatory response to cyanoacrylate glues.

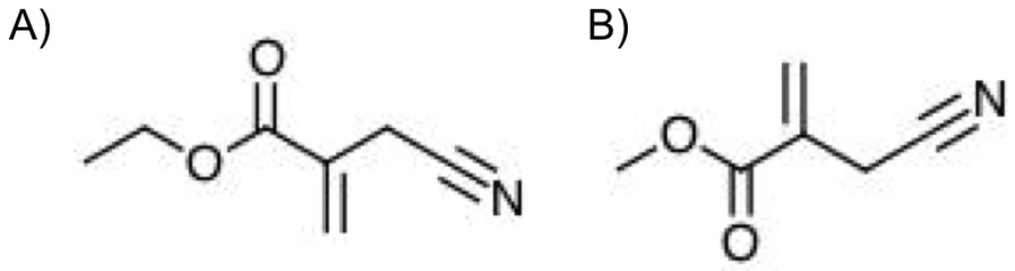

Figure 2. The structures of short-chain cyanoacrylate tissue adhesives, (A) ethyl-2-cyanoacrylate and (B) methyl-e-cyanoacrylate.

2.1.1. Notable advances in cyanoacrylate adhesives

Recently, cyanoacrylates were used in the development of self-healing materials. Self-healing materials are those that are engineered to prevent failure through an autonomous repair mechanism. In the first reported use of cyanoacrylate in this area, the polymer was combined with acrylate bone cement, poly(methyl methacrylate) (PMMA) [23]. In this work, polyurethane shells were used to encapsulate 2-octyl cyanoacrylate monomers, which were embedded in the PMMA to form a composite upon cure. The 2-octyl cyanoacrylate was released from the polyurethane shells and polymerized upon contact with moisture. In doing so, it filled cracks and defects that formed inside the PMMA, reinforcing the matrix. Incorporation of the 2-octyl cyanoacrylate slowed down progressive crack propagation under loading compared with unreinforced PMMA cement. In subsequent work [24], it was shown that reinforced specimens were able to withstand twice as many repetitive loading cycles before failure compared with unreinforced specimens. Cyanoacrylate films with a broad range of nanostructured architectures were also created [25]. In order to achieve this, N-octyl-2-cyanocrylate was electrospun and an air pump was used to precisely direct the nanosized polymer fibers to a wound bed. The deposited fibers formed a flexible, high strength membrane that was used to effectively arrest bleeding in in vivo models of liver and lung resection.

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2.2. Protein adhesives

2.2.1. Gelatin-based

Gelatin is derived from the hydrolysis of collagen [6] and widely used in biomedical applications because of its biocompatibility and degradability [26]. Gelatin is capable of forming physically cross-linked hydrogels, but the mechanical strength is low and the hydrogels do not possess adhesive properties [27]. For this reason, gelatin-based tissue adhesives use chemical cross-linking and often also include additional polymer additives.

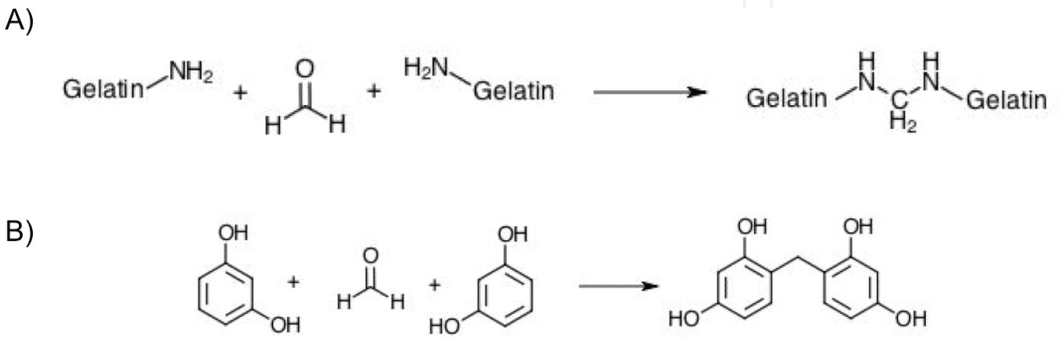

Figure 3. (A) The chemistry of cross-linking gelatin with formaldehyde and (B) the network that is formed by the reaction of resorcinol with formaldehyde.

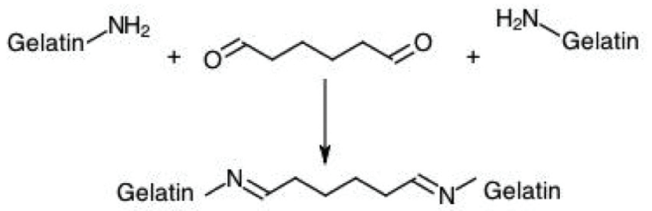

Figure 4. The cross-linking of gelatin with glutaraldehyde via a Schiff's base reaction.

The earliest gelatin-based adhesive is composed of gelatin, resorcinol, and formaldehyde. Referred to as GRF glue, it forms a seal in situ because the formaldehyde cross-links with the gelatin (**Figure 3A**) and the resorcinol (**Figure 3B**) to form a network. The resorcinol is added to augment the mechanical properties of the adhesive [10]. The composition of GRF glue comprises 18% by weight of formaldehyde, despite the well-known concerns over its toxicity [1, 6]. Braunwald et al. [28] evaluated GRF glue in an in vivo canine model, noting that the degree of irritation caused by the formaldehyde depended on the vascularity of the tissue. Excess formaldehyde may be diluted and washed away in areas where there is high enough blood flow. However, due to concerns over the safety of GRF glue, the formulation was later revised to replace a portion of the formaldehyde in the adhesive with glutaraldehyde, which is less histotoxic [29, 30]. Glutaraldehyde forms a Schiff's base with the free amines on gelatin, forming cross-links in the network just as formaldehyde does (**Figure 4**). This updated formulation was called gelatin-resorcinol-formaldehyde-glutaraldehyde (GRFG) glue. When

applied in the liver of rats, no evidence of necrosis was found and it was shown to be an effective sealant and hemostat. Another group modified the GRFG formulation by adding 2.5% sodium carboxymethylcellulose (CMC). This created a "jelly" consistency for the glue, helping to prevent migration away from the target tissue site. The jelly was applied in humans to seal air leaks and found safe for shallow cuts in the lung [31]. Despite some successful outcomes, glutaraldehyde is technically classified as a toxic substance, so safety concerns prevent approval of GRF/GRFG glues by the FDA in the United States [32, 33].

2.2.2. Advances in gelatin-based adhesives

Researchers have looked into alternative cross-linkers for gelatin that are potentially less toxic than glutaraldehyde and formaldehyde. Rapidly polymerized elastic gelatin networks were also produced via photochemical cross-linking in the presence of ruthenium II trisbipyridyl chloride $[RuII(bpy)_3]^{2+}$ catalyst and ammonium persulfate oxidant [34]. Visible light causes the photolysis of the $[RuII(bpy)_3]^{2+}$. The Ru(II) and sulfate radicals oxidize tyrosine residues, present on gelatin, allowing formation of an intermolecular dityrosine cross-link. When gelatin was modified with additional phenolic (tyrosine-like) residues, the sealant stiffness increased by a factor of five and swelling was restricted compared with gels made from unmodified gelatin due to the increased cross-linking density [35]. Blends of modified and unmodified gelatin can give tunable elasticity and elastic modulus [33]. The reagents were found to be non-toxic at the concentrations used to make the gels [35].

In another study, cholesterol chloroformate was used to partially convert the amino groups on the gelatin to cholesterols. Cross-linking occurred by mixing a combination of cholesterol-modified gelatin with disuccinimidyl tartrate. Covalent bonding also occurred with collagen in the surrounding tissue extracellular matrix (ECM). Moreover, adhesion was enhanced due to the hydrophobic cholesterol groups, which promoted polymer chain penetration into the tissue and anchoring to cell membranes [36].

N-(3-dimethyl-aminopropyl)-N'-ethylcarbodiimide hydrochloride, a water-soluble carbodiimide (WSC), was shown to be an effective cross-linker of gelatin, but high concentrations (20 mg/mL) negatively impacted cell viability. The group was able to decrease EDC concentrations in the adhesive by functionalizing the gelatin with N-hydroxysuccinimide (NHS) groups [37]. N-hydroxysuccinimide (NHS) esters are known to react with primary or secondary amines (**Figure 5**). In this reported study, the addition of low concentrations of NHS (1 mg/mL) allowed the EDC concentrations to be decreased to 10 mg/mL without compromising adhesive strength and maintaining high cell viability (89–100%) [37].

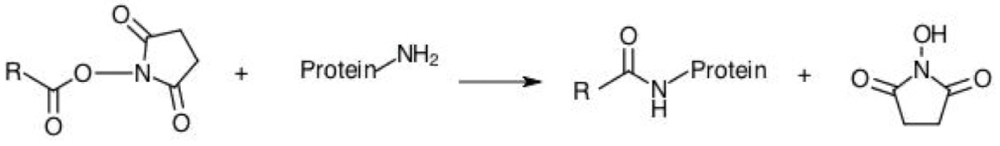

Figure 5. Reaction scheme for NHS ester conjugation to a primary amine.

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Another approach involves the use of enzymatic cross-linking. The advantage of this route is that the gelation occurs under physiological conditions. Transglutaminase are ubiquitous in nature and catalyze the reaction between lysine and glutamine, resulting in cross-linking of proteins (**Figure 6**). Chen et al. [38] used this enzyme to introduce cross-links into gelatin under moist conditions. The adhesive did not cause cell death in rat retinal tissue when applied in vivo for 2 weeks. It is important to note that since the cross-linking reaction causes release of ammonia, local tissue damage or inflammation is possible.

Figure 6. The cross-linking of gelatin via the enzyme transglutaminase [38].

2.2.3. Albumin-based adhesives

Another type of protein-based adhesive is based on albumin and glutaraldehyde. Albumin is an abundant protein found in the blood of mammals. Glutaraldehyde cross-links albumin to itself and to the proteins in the surrounding tissue at the repair site via a Schiff's base reaction. The albumin network forms a rigid, brittle solid [29]. Bioglue® is a bovine albumin-based glue available on the market that is approved for cardiac and vascular surgery [39]. Bioglue is less histotoxic than GRF glue and has superior bonding ability [40, 41]. Bioglue was successfully used to clinically treat bronchopleural fistula [42], partial renal nephrectomy [43], and vascular anastomoses [44]. Due to the presence of glutaraldehyde, there are still safety concerns with its application in certain areas of the body with high cellularity. For instance, adverse effects were reported on nerve function in a porcine model when the adhesive was applied directly onto the phrenic nerve [45].

2.2.3.1. Advances in albumin-based adhesives

De Somer et al. [46] developed an autologous albumin glue to avoid the immune response associated with bovine components. Fresh human plasma was ultrafiltered to concentrate the plasma proteins, which were then combined with glutaraldehyde. The autologous glue exhibited higher compliance than rigid Bioglue, likely due to the presence of fibrinogen in the concentrated blood plasma. The disadvantage of this method is that it requires 60 min of preparation time once the plasma is obtained. As an alternative to cross-linking with glutaraldehyde, another group prepared a modified tartaric acid with two active NHS ester groups and combined it with human albumin [47]. Subcutaneous implantation in mice indicated the adhesive was safe, eliciting a mild inflammatory response, but the results were not compared side by side with an adhesive cross-linked with glutaraldehyde.

2.2.4. Fibrin adhesives

Fibrin adhesives work by mimicking the biochemical reactions of the last stage of clotting [48, 49]. The resulting clot at the site of repair is a cross-linked network of proteins that also forms covalent linkages with the surrounding tissue, allowing adhesion to occur. Fibrin glues are applied as hemostats to stop bleeding, in addition to being used as sealants to achieve closure [6].

In general, fibrin sealants are composed of three major protein building blocks: fibrinogen, thrombin, and factor XIII, which are derived from human or bovine plasma [1]. Upon mixing the constituents, the thrombin converts the fibrinogen to fibrin monomers. The fibrin monomers will self-assemble into a fibrin polymer, forming a network weakly held together by hydrogen bonds. At the same time, thrombin activates factor XIII, which catalyzes the formation of cross-links in the fibrin polymer and between the polymer and the surrounding tissue, providing a stable the clot [49–51]. The sealants also contain calcium ions, since they are required for the reactions in the clotting cascade [52]. Commercial fibrin sealants, available in the United States, have components derived from blood banks and include TISSEEL®, Crosseal™, Beriplast®, and Evicel® [53]. Because fibrin glue is one of the oldest developed adhesives, it has a long list of reported applications, such as the repair of nerves [54], gastrointestinal tracts [55], topical wounds [56], and ophthalmology [57].

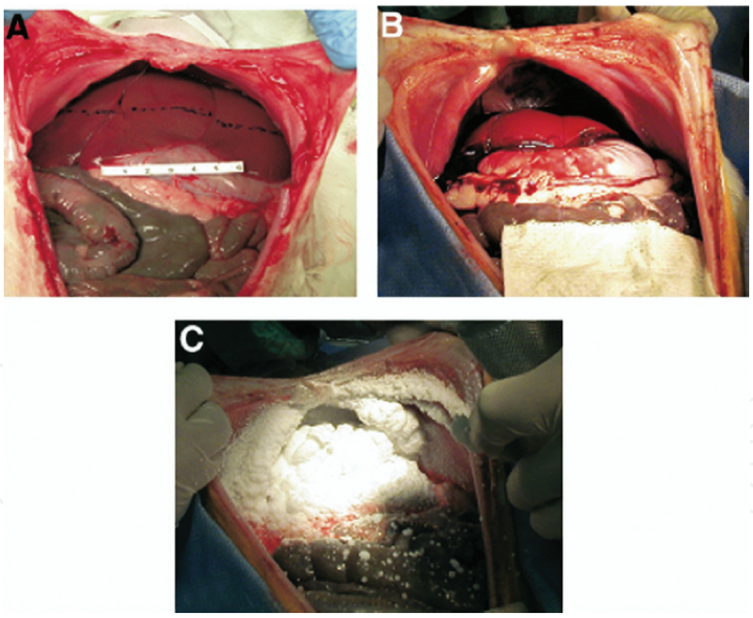

Figure 7. (A) Rabbit liver lobes shown before injury, (B) after the resection injury, and (C) after FSF application [62]. Copyright 2008. Reproduced with permission from Elsevier Inc.

The components are either lyophilized powders that require reconstitution prior to use, or liquid products that are stored frozen then thawed and mixed together in the surgical field [58]. The fibrinogen and thrombin components, supplied separately, can be applied successionally or simultaneously, with a dual-syringe or spray device. The material properties of the clot, and

thus its clinical performance, will be determined by its elasticity, tensile strength, and adhesion strength (Kjaerd 2000). For this reason, several groups have studied the polymerization and cross-linking characteristics of fibrin sealants. It was reported that key factors to ensuring glue performance are adequate fibrinogen content, effective mixing of the components, and maintenance of factor XIII activity [59]. Sierra et al. [60] found that the tensile strength, modulus of elasticity, burst strength, and failure strength, all increased with fibrinogen concentration.

Spray application of fibrin adhesive may have advantages over simultaneous and sequential drip application because spray application results in the most homogenous clots [61] and allows for better control over severe bleeding over large areas, which can occur after trauma. A self-expanding fibrin sealant foam (FSF) was characterized [62]. For preparation, the sealant was placed in a pressure-resistant bottle with liquefied gas propellant, which converted the fibrin components to foam at atmospheric pressure. It was used to arrest bleeding in a rabbit liver resection (**Figure 7**).

As another option, fibrin sealants have been made available as ready-to-use lyophilized powders that can be stored at room temperature. Fibrocaps (Raplixa; ProFibrix BV, Leiden, The Netherlands, a subsidiary of The Medicines Company) is dry powder thrombin and fibrinogen that can be applied straight to the wound site to form the clot [58]. For compressible injuries, lyophilized fibrinogen and thrombin have been combined with gauze (Larson 1995), as well as collagen sheets (Nistor 1997).

2.2.4.1. Notable advances in fibrin sealants

Fibrin glues are well known for being completely non-toxic and biodegradable [1], yet there are some disadvantages that limit their applicability in advanced applications. First, degradation in vivo will occur within days, a time frame that could allow for rebleeding. Aprotinin is a molecule consisting of 58 amino acids that is added to commercial fibrin glues to slow down its cell-mediated degradation [63]. When simply codissolved in a fibrin gel, aprotinin can freely diffuse out due to its small size. To prolong degradation time further, aprotinin has been covalently conjugated to fibrinogen [64]. Varying the levels of conjugated aprotinin allowed for control of the degradation time.

A second drawback to fibrin sealants is that they are mostly derived from human donors, or from the blood of animals with compatible clotting systems, limiting their availability, making them expensive, and introducing the possibility of transmission of blood borne pathogens. One option that has been investigated is deriving the protein components from animals where the evolutionary distance from humans is large, thus allowing for minimized risk of disease transmission. Fibrin components have thus been derived from salmon [65, 66] and crotalus durissus terrificus snake venom [67]. Another option is to use completely autologous fibrin glue. The Vivostat® System is an automated device that allows for the production of 5 mL of fibrin sealant from 120 mL of the patient's blood [68]. When Kjaergard et al. [69] compared its performance to commercially available Tissucol® and Beriplast®, autologous glue exhibited a higher elongation at break. However, the sealant takes about 30 min to prepare. Another report described a totally recombinant human sealant that exhibited comparable hemostatic efficacy to a commercial plasma-derived sealant in a porcine hepatic excision model [70].

A third important drawback to fibrin sealants is the poor adhesion properties, especially in wet environments, and low mechanical properties compared with most elastic tissues [2]. Researchers have been developing fibrin glues with alternative structures that lead to improved physical properties. A genipin cross-linked fibrin adhesive was described that was used to seal small defects in the annulus fibrosus of the intervertebral disc [71]. Genipin is a plant-based chemical cross-linker reactive with amines and reported to have low cytotoxicity [72]. Fibrin gels that were cross-linked with genipin were dimensionally stable over the 21-day in vitro study and exhibited higher shear stiffness than fibrin gels that were not cross-linked with genipin. In another study, elastic gels were produced via photochemical cross-linking of fibrinogen using $[RuII(bpy)_3]^{2+}$ and ammonium persulfate. Overall, fibrinogen gels cross-linked with this method are reported to have a higher tensile strength than Tisseel® [73].

2.2.5. Synthetic hydrogel sealants

2.2.5.1. Photocrosslinkable polyethylene glycol sealants

Although natural materials such as fibrin have the advantages of biodegradability and biocompatibility, the various shortcomings in fibrin properties have led to the development of synthetic polymer networks [74]. Engineers have more control over mechanical and degradation properties than with natural materials because polymer structure can be tailored. In these sealants, hemostasis is achieved using reagents that cross-link the polymer network, while binding with tissue, to close the injured site. Poly(ethylene glycol) (PEG) is an FDA-approved material that has been extensively used as the main component in synthetic adhesives [32].

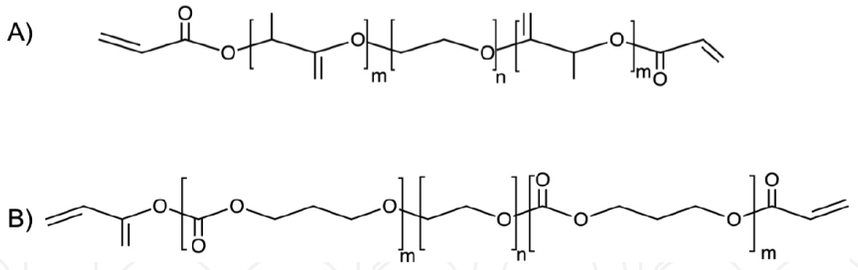

Figure 8. FocalSeal is formed from two different aqueous solutions of reactive macromers, (A) PLAm-PEGn-PLAm diacrylate and (B) PTMCm-PEGn-PTMCm diacrylate.

FocalSeal® was FDA-approved in 2000 for sealing air leaks after lung surgery. The sealant is provided to surgeons in two parts (primer and sealant). The primer is an aqueous solution of a triblock copolymer of poly(lactide) and polyethylene glycol (PLA-PEG-PLA) with acrylated end groups (**Figure 8A**). The sealant is an aqueous solution of poly(ethylene glycol)-co-trimethylene carbonate-co-lactide (PTMCm-PEGn-PTMCm) with acrylated end groups and a photoinitiator, eosin Y (**Figure 8B**). The primer and sealant solutions are combined immediately before application to the target area in the body. Upon exposure to light (450–550 nm), the macromers polymerize to form a cross-linked network due to the reaction between the acrylate groups [75]. The adhesion occurs due to mechanical interlocking, in other words, the

liquid monomer solution infiltrates the pores and irregularities in the tissue surface, and, upon gel formation, adhesion occurs [32]. Over time, the lactide and trimethylene carbonate groups degrade by hydrolysis and the PEG chain are cleared by the kidneys. The sealant takes 3–4 weeks to resorb [1]. FocalSeal was evaluated as a dural substitute in a canine craniotomy model [75]. All treated sites remained free of leaks of cerebrospinal fluid (CSF) for the 56-day study. In a later clinical trial, 100% of the 46 patients receiving the dural sealant after cranial surgery remained free of CSF leaks [76]. FocalSeal was used with 100% success as a supplement to sutures or staples to repair air leaks after pulmonary resection in pigs [77]. It was also used successfully to repair retinal breaks [78].

A drawback to photopolymerization is that it may not be ideal for all parts of the body, as ultraviolet light cannot infiltrate tissue located greater than 5 mm of depth into the body [79]. Further, photoactivation makes application of the sealant difficult in the case of a hemorrhage [80]. There is a danger of releasing free radicals into the physiological environment [1]. Another disadvantage of FocalSeal specifically is that it can swell up to 300% of its original weight [81]. This could limit its application in areas of the body where there is potential for nerve compression [82].

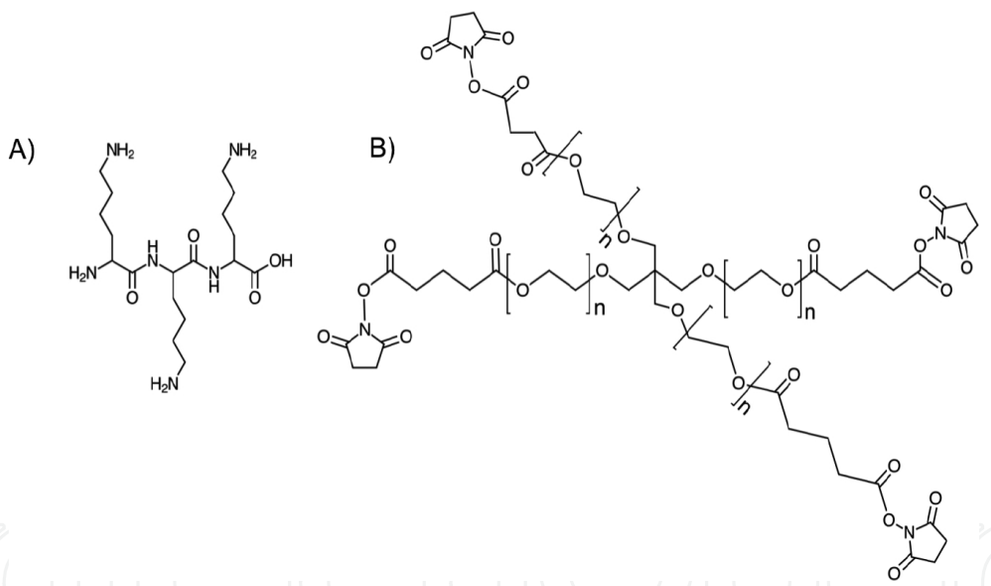

Figure 9. The reactive components of DuraSeal, (A) trilysine and (B) pentaerythritol poly(ethylene glycol) ether tetrasuccinimidyl glutarate.

DuraSeal® is a two-component system of trilysine (a tetramine cross-linker, **Figure 9A**), dissolved in a pH 10 borate buffer. The second is pentaerythritol poly(ethylene glycol) ether tetrasuccinimidyl glutarate (a 4-arm PEG encapped with N-hydoxysuccinimide (NHS) esters), dissolved in a sodium phosphate buffer (pH = 4) (**Figure 9B**) [1]. Upon mixing, the trilysine reacts with the NHS ester groups, generating the cross-linked hydrogel. In addition, upon contact with the amine groups in the extracellular matrix, the NHS-functionalized PEG chains will covalently bond with the surrounding tissue, providing adhesion combined with mechanical interlocking. Degradation takes place over 4–8 weeks [83]. One of the earliest reports

of DuraSeal was in 2003 [84], when it was characterized to be an effective adjunct to sutures for dural closure in a canine model. A clinical trial with DuraSeal was reported in 2011 [85]. A total of 158 patients underwent spinal surgery requiring dural incision. 100% of the 102 patients that received DuraSeal combined with sutures had complete closure, compared with only 64% in the control group that received sutures alone.

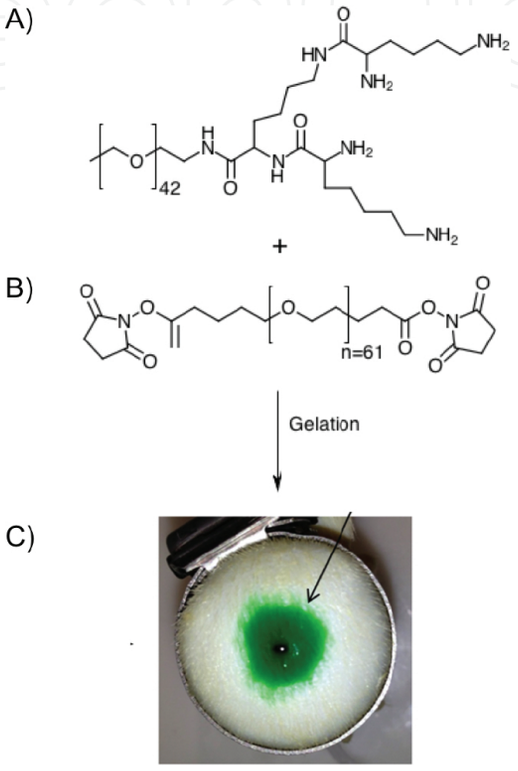

Figure 10. The combination of (A) a PEGylated lysine dendron and (B) PEG succinimidyl valerate results in the formation of a PEG-LysNH2 hydrogel, shown in (C) dyed with green food coloring [87]. Copyright 2015. Reproduced with permission from Biomed Central.

After gelation, DuraSeal can swell up to 50% after application [1]. To minimize swelling, another formulation was developed, DuraSeal® Xact Adhesion Barrier and Sealant System (DSX). Compared with DuraSeal, it has an increased cross-link density by modification of the ratio of PEG to trilysine [1, 86]. Villa-Camacho et al. [87] reported a novel sealant that uses similar chemistry to DuraSeal. Here, a PEGylated lysine dendron in dissolved in buffer at pH 9 is combined with solubilized PEG succinimidyl valerate at pH 6.5 (**Figure 10**). The hydrogel forms spontaneously upon mixing. The ability of the adhesive to withstand pressures analogous to human arterial pressures was demonstrated ex vivo.

CoSeal™ is a two-component tissue sealant. The first component 20% (w/v) buffer solution of a 4-arm PEG polymer of 10 kDa molecular weight end capped with thiol groups (pH 9.6) (**Figure 11**), and the second component is a 20% (w/v) buffer solution of pentaerythritol poly(ethylene glycol) ether tetrasuccinimidyl glutarate (pH 6.0) (**Figure 9B**). The components

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are reactive with each other and the proteins in the surrounding ECM [88], providing adhesion via chemical bonding and mechanical interlocking. The hydrogel degrades within several weeks due to hydrolysis. In one of the earliest studies with CoSeal, it lessened blood loss and time to hemostasis in bleeding rabbit arteries compared with using a tamponade [89]. CoSeal has been reported as cumbersome to use because it is supplied as a powder, which requires mixing back and forth 20 times to dissolve [90]. It has also been reported to swell to 400% of its original size [1, 90]. Likely related to the high swelling characteristics, the mechanical strength of CoSeal has been found to be weaker than DuraSeal and other commercially available protein-based and cyanoacrylate sealants [30].

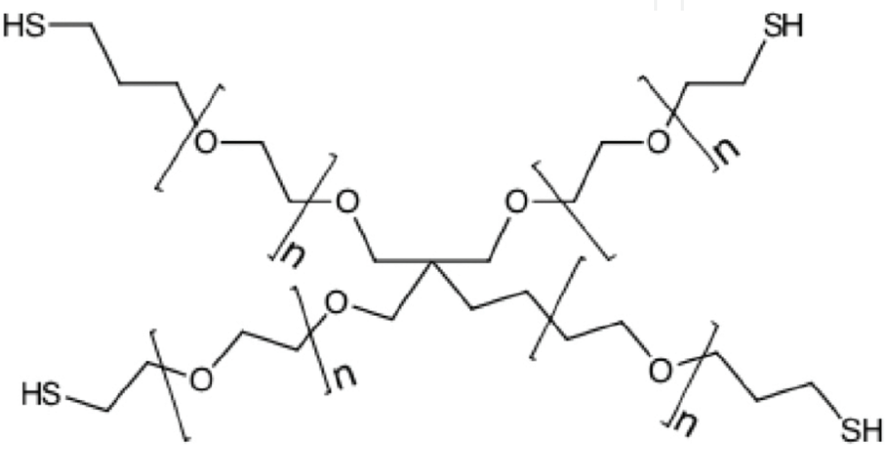

Figure 11. Structure of thiol end capped 4-arm PEG used in CoSeal®.

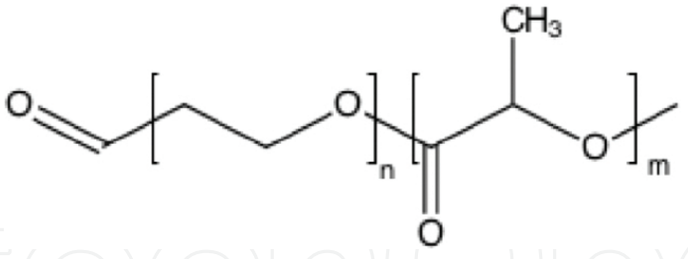

Figure 12. The structure of aldehyde-terminated poly(ethylene glycol)-poly(D,L-lactide) (PEG-PLA) block copolymers prepared by Murakami et al. [80].

Another group of PEG adhesives uses Schiff's base chemistry as the cross-linking reaction. For example, an 8-arm PEG molecule was functionalized with either aldehyde or amine groups. When combined in water, it spontaneously formed gels because of the reaction between the aldehyde and free amine groups [91]. Gels formed from PEG arms that were 10 kDa in size were stiffer than those formed from 20 kDa due to higher cross-link density. In vitro lap shear testing showed that the adhesive was stronger than fibrin glue (Tissucol). It swelled to about 200% of its original weight, which is less than CoSeal and FocalSeal. The results of a direct contact cell assay with L929 fibroblasts showed no cytotoxicity associated with the cured gels. Aldehyde-terminated poly(ethylene glycol)-poly(D,L-lactide) (PEG-PLA) micelles were also

prepared (**Figure 12**) by dissolving the block copolymer in aqueous media. A hydrogel forms in ~2 s when a polyallylamine is added to the micelles. Adhesive strength of the network was found to be proportional with aldehyde concentration, with the strength of the high aldehyde content adhesives comparable to fibrin glue [80].

2.2.5.2. Notable advances in PEG adhesives

Researchers continue to innovate systems that allow them to achieve high adhesive strengths, ease of use, fast curing, biodegradability, and biocompatibility with alternate methods of cross-linking. Hu et al. [92] incorporated peptide substrates of transglutaminase into linear or branched polymers of PEG. The in situ formed gels exhibited adhesive strengths to porcine skin comparable to that of fibrin glue [92].

Systems have been developed that are combinations of synthetic and natural components. These have potential to exhibit improved biocompatibility compared to systems that are completely synthetic. For instance, cells do not adhere to PEG hydrogels. Hynes et al. [93] chose poly(L-lysine) (PLL) to be incorporated into PEG structure because the charged side chain promotes cell survival and adhesion. Macromers of PEG/PLL, shown in **Figure 13**, were formed hydrogels via photopolymerization and shown to support survival and differentiation of neural precursor cells. Another group [94] reported a gelation system consisting of the following components: calcium-loaded liposomes composed of 1,2-bis(pal-mitoyl)-sn-glycero-3-phosphocholine (DPPC), human recombinant factor XIII, thrombin, and 4-arm PEG, each arm terminating in a 20-mer sequence derived from fibrin. Heating the system to 37°C causes the liposome bilayer to melt, releasing the calcium and activating factor XIII, causing gelation to occur in 9 min.

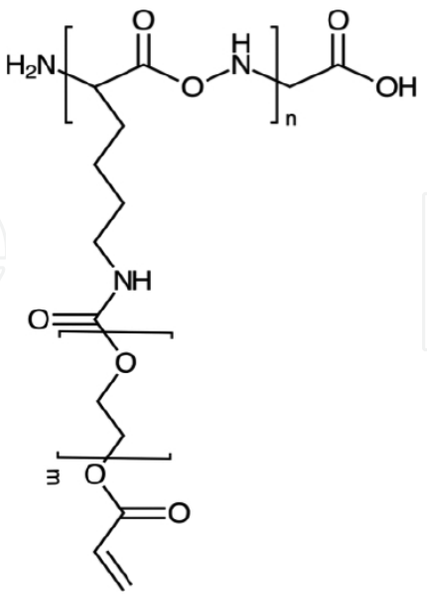

Figure 13. The molecular structure of PEG/PLL macromers for the formation of photopolymerized hydrogels developed by Hynes et al. [93].

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Besides improving biocompatibility, researchers are working on developing stronger PEG adhesives. For example, by combining silk, which has a high mechanical strength, with PEG, a sealant was produced with fast curability, superior adhesion strength to CoSeal, and swelling ratios of only 60–70% due to the hydrophobicity of the silk [90].

2.3. Polysaccharides

In situ forming tissue sealants have also been prepared from natural polysaccharides, which are composed of repeat units of naturally occurring sugars, making them inherently biodegradable non-immunogenic [1]. Like synthetic polymers, the chemical structure of polysaccharides can be modified to induce spontaneous or light-triggered gelation in situ and enhance adhesion strength with surrounding tissue.

Photopolymerization of polysaccharides that are functionalized with acrylate or methacrylates along the backbone is one way to achieve in situ gel formation. In this case, the polysaccharide may be applied in liquid form, where it will penetrate the crevices in the tissue. Upon polymerization, reacted acrylates or methacrylates form covalent cross-links and the resulting gel seals the area [95]. An example is the methacrylation and photopolymerization of hyaluronic acid (HA), a linear polysaccharide consisting of alternating β-(1–4) linked 2-acetamine-2-deoxyglucose and β (1–3) linked d-glucuronic acid (**Figure 14A**). Methacrylate-functionalized hyaluronic acid (HA) (**Figure 14B**) was applied to corneal lacerations in rabbits to allow for network formation upon irradiation [96]. This produced a flexible clear patch that sealed 97% of the corneal lacerations and retained its shape and size for the duration of the 7-day study. The authors hypothesized that the high molecular weight, entangled 3D structure of the HA slowed down its enzymatic degradation in vivo.

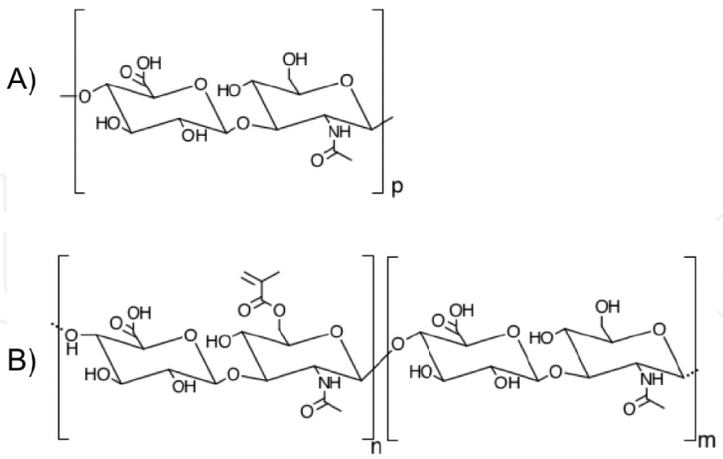

Figure 14. Chemical structure of (A) hyaluronic acid and (B) methacrylated hyaluronic acid.

As an alternative to photopolymerization, oxidation of polysaccharides to aldehyde groups using sodium periodate [97] is widely applied for forming polysaccharide networks. The aldehyde functionalities readily react amine-containing molecules via Schiff's base reaction to internally cross-link a polysaccharide to itself and surrounding tissue ECM [7]. Sodium

alginate (**Figure 15**) derived from brown algae, functionalized with both methacrylate and aldehyde groups, was investigated as a tissue sealant. Cross-linking of the methacrylate groups was achieved by visible light. Simultaneously, the aldehydes reacted with the amines in the surrounding ECM, allowing for covalent attachment to surrounding tissue. Gels that were methacrylated, but not oxidized, maintained mechanical integrity during burst pressure tests, but delaminated from the substrates easily. On the other hand, materials that received both methacrylate and aldehyde groups did not exhibit delamination before failure [98].

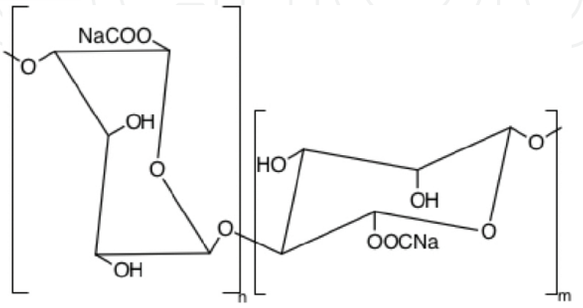

Figure 15. The chemical structure of sodium alginate.

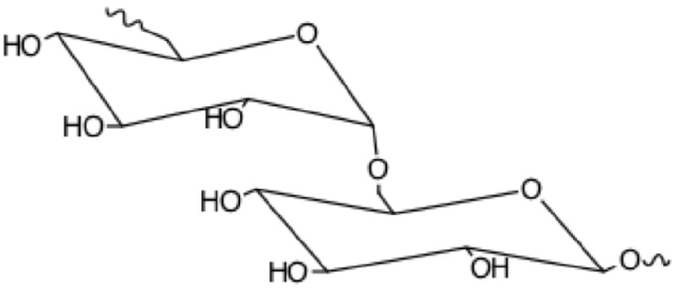

Figure 16. The chemical structure of dextran.

Dextran is another polysaccharide that has been extensively investigated as a sealant in various combinations with other polymers. Dextran is a microbial product consisting of about 95% α-1,6-linked d-glucopyranose and 5% α-(1,3) linkages (**Figure 16**). Araki et al. developed a new bioadhesive that forms from the reaction of dextran aldehyde and ε-poly(L-lysine). The components were applied in a pulmonary air leakage model in a canine model. The sealant had significantly higher burst pressure than fibrin glue and degraded more slowly [99]. Structure-property relationships in this adhesive were studied further [8]. It was found that as the degree of oxidation (DOO) of the dextran increased, gelation time decreased. Gelation times ranged between 3 s (40% oxidation) to 60 s (12% oxidation) [8]. Increased DOO of dextran was also associated with a slower degradation time [100].

In another study, dextran aldehyde was cross-linked with either 8-arm star PEG amine or linear PEG diamine [101]. A higher stability cohesion was observed for gels made from the 8-arm star PEG because the larger number of available amines allowed for a higher degree of cross-

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linking. Another group, Bhatia et al. [102] studied adhesives based on dextran aldehyde and 8-arm PEG. They reported the system to cure in less than 1 min, adhere in a water environment, and degrade hydrolytically. The adhesive was utilized to seal a 5-mm corneal incision in eyes of New Zealand white rabbits [103]. They found that sealants produced from higher polymer contents led to better sealing and higher leak pressures. Degradation occurred within three days, appropriate time frame for corneal epithelial healing, and no cytotoxicity was observed from the cured adhesive. In a follow-up work, the degradation time was extended to 5 days by using an 8-arm PEG containing two primary amine groups at the end of each arm, instead of one [104].

Chondroitin sulfate (CS), a constituent of cartilage and corneas, is comprised of alternating glucuronic acid and N-acetyl-galactosamine groups (**Figure 17**) [1]. CS was functionalized with succinimidyl succinate (CS-NHS) and combined with 6-armed polyethylene glycol (PEG) amine as a corneal sealant [105]. This adhesive was developed as an alternative to using CS aldehyde, hypothesizing that using a CS with an intact backbone helps to preserve its biological activity. Upon mixing, the materials gelled within 1–2 min and cured polymers exhibited no cytotoxicity in vitro with rabbit primary epithelial, stromal, and endothelial cells. No adverse effects were found with implantation into in vivo swine cornea.

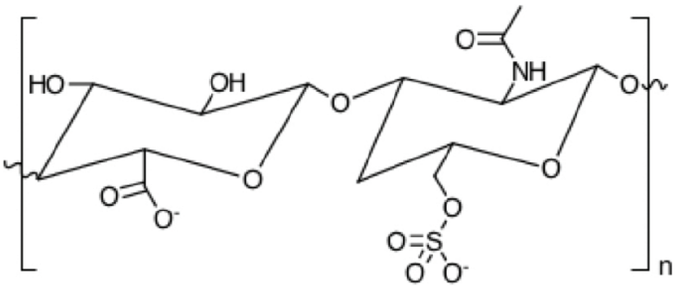

Figure 17. The chemical structure of chondroitin sulfate.

2.3.1. Notable advances in polysaccharide adhesives

Adhesives made out of chitin derivatives have the potential to be valuable additions to the presently developed spectrum of polysaccharide-based sealants. Chitin is comprised of repeat units of 1,4 b-linked N-acetyl-D-glucosamine (**Figure 18A**). Chitosan is formed from partially deacetylated chitin [106] (**Figure 18B**). Since chitin is highly hydrophobic and completely insoluble in water, chitosan is more often used in biomedical applications. Chitosan has been shown to have a number of biological advantages, including being beneficial for wound healing [107, 108], inherent hemostatic ability [109], and antimicrobial activity [110, 111]. Chitosan has adhesive properties due to the positively charged amino groups, which interact with negative charges in mucus [112] and cell membranes [113]. However, one downside to chitosan is that it has limited solubility in water at neutral pH. Thus, researchers modify chitosan with side groups that enhance solubility in water at physiological conditions. For example, chitosan was modified with lactose groups to enhance water solubility [106] and cross-linked in situ with the addition of photoreactive azide groups. The resulting rubber-like

adhesive was an effective sealant in rabbit arteries and lungs. In another study, a new adhesive was developed based on 2-hydroxy-3-methacryloyloxypropylated carboxymethyl chitin derivatives (HMA-CM-chitin) and embedded chitosan nanofibers. It was shown in vitro to have comparable strength to cyanoacrylate since the nanofibers provided gel network reinforcement [108].

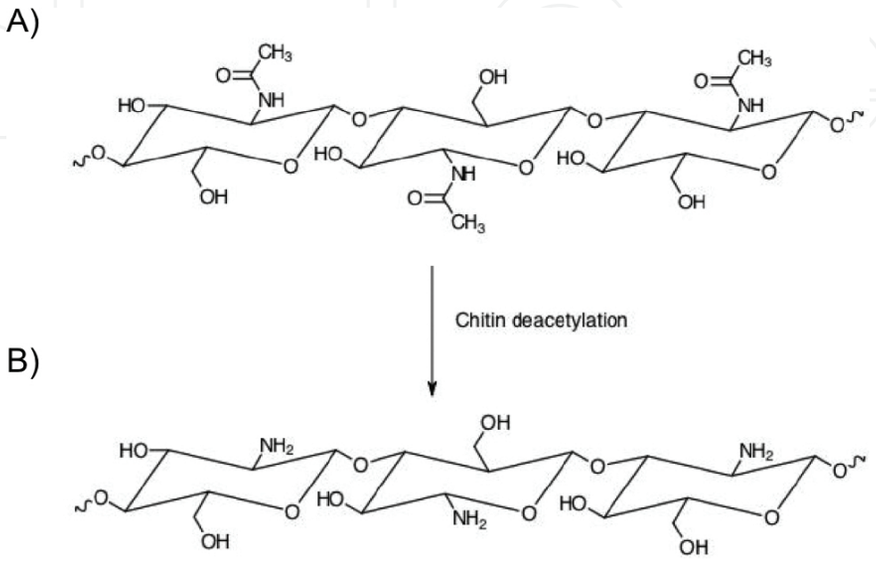

Figure 18. The structure of (A) chitin and (B) partially deacetylated chitin, also referred to as chitosan.

2.4. Nature-inspired materials

2.4.1. Mussel-inspired sealants

The most extensively investigated class nature-inspired materials uses mussel adhesive proteins (MAPs). Mussels can adhere strongly to underwater structures, even in environments with high mechanical stresses. Mussels attach to surfaces because they secrete a thread-like adhesive called byssus, which is composed of 25–30 different types of MAPs [114, 115]. An amino acid residue in these proteins, tyrosine, is posttranslationally modified to 3,4-dihydroxy-phenylalanine (DOPA) residues, which contains a catechol group (**Figure 19**). Catechols can hydrogen bond with other catechols [116], as well as amino, hydrogen and carboxyl resides [117]. Catechols can be oxidized by metal ions or enzymes to form quinones (**Figure 19**). Quinones form covalent bonds with amine or thiol groups [114, 116, 118, 119]. Finally, the catechol group complexes with multivalent ions, such as Fe3+ [120, 121] to form networks. Researchers have been developing materials that recapitulate these mechanisms in order to achieve strong bonding in wet environments.

Extracting MAPs from mussels or genetically engineering the proteins can result in low yields [122]. Thus, catechol pendant groups have been attached to the backbone of natural and synthetic polymers to yield biomimetic adhesives. Catechol auto-oxidizes at slightly alkaline pH >8, or in the presence of oxidizing reagents, such as periodates [123]. Researchers use these

methods to produce quinones in situ, which leads to covalent bonding with tissue. In some of the early work with mussel-inspired synthetic polymers, linear and branched PEGs were functionalized with either 1,2, or 4 DOPA end groups [124]. Gels were formed with the use of three different oxidation reagents: sodium periodate, horseradish periodate, and mushroom tyrosinase. Rapid gelation occurred when 2 or more DOPA functionalities were present on the PEG molecule. However, PEG-based hydrogels can act brittle, fracturing at low elongation [125]. Improvements in the mechanical properties of PEG-catechol hydrogels were achieved by using block copolymers of PEG and poly(caprolactone) with DOPA groups. Because PCL is hydrophobic, it prevented swelling of the hydrogels, so they were not as fragile. Moreover, PCL made the gels less brittle, since it has a high fracture strain [126]. In another work, poly[(3,4-dihydroxystyrene)-co-styrene] copolymers (**Figure 20**) were prepared [119]. The adhesive characteristics in the presence of periodate on plastic and wood surfaces were investigated and there was found to be an optimal pendant catechol concentration along the polymer backbone. When the concentration of catechol was too low, there were insufficient cross-linking sites available at the surface. Too high a concentration would bias the system toward internal cross-linking, and surface attachment suffered.

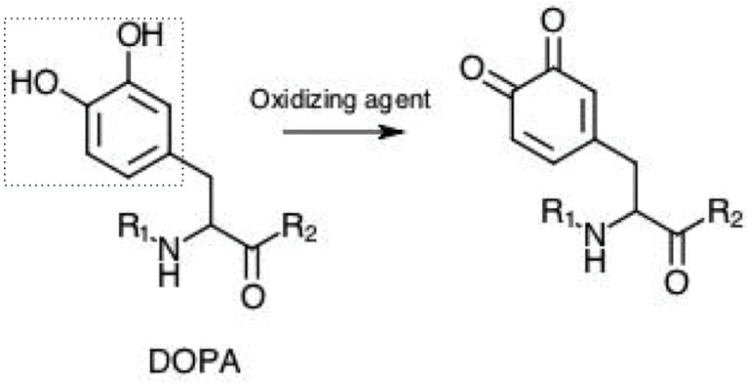

Figure 19. (A) 3,4-Dihydroxy-phenylalanine (DOPA) residues, with the catechol group indicated by the dotted line and (B) quinone formed from the oxidation of the catechol group.

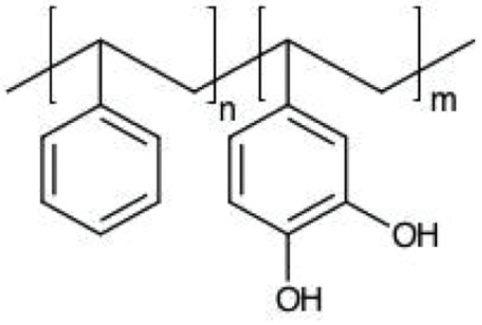

Figure 20. The chemical structure of poly[(3,4-dihydroxystyrene)-co-styrene] copolymers developed by Matos-Perez et al. [119].

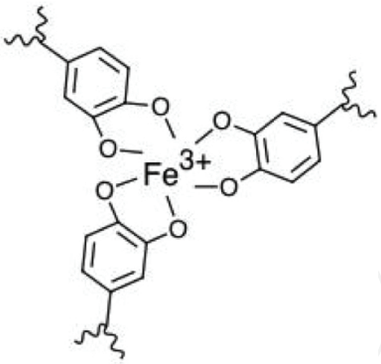

Figure 21. Fe^{3+} serves as a rapid cross-linker for DOPA-containing polymers by forming complexes with the catechol groups.

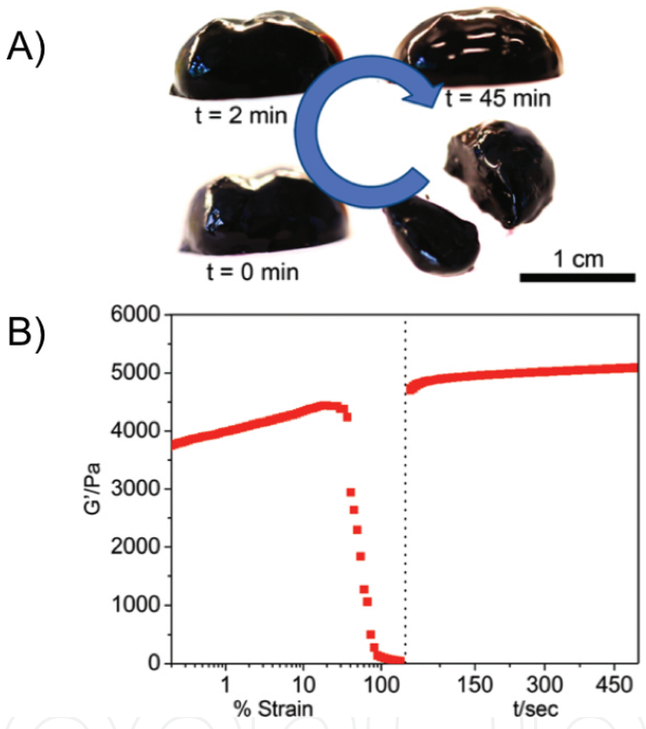

Figure 22. Qualitative (A) and quantitative (B) recovery tests for hydrogels composed of polyallylamine in solutions of $FeCl_3$. In the qualitative tests (A), a blob of hydrogel was fractured and the fragments healed upon contact with each other. This process was quantified with dynamic oscillatory rheology (B) by shearing a hydrogel at increasing strain at 1 s^{-1} from 0.01 until 200% strain. The recovery was recorded at 1% strain and 1 s^{-1} [120]. Copyright 2013. Reproduced with permission from American Chemical Society.

Oxidizing reagents like periodate are expected to exhibit toxicity in biological systems [118]. Interestingly, DOPA in its unoxidized state has bioadhesive properties [114]. For instance, functionalization of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers with DOPA end groups was performed. Gelation of these polymers in situ occurred because of the temperature-induced phase transition of the block copolymer. The results showed significantly improved adhesion over PEO-PPO-PEO alone

[118]. Ryu et al. functionalized PEO-PPO-PEO with terminal thiol groups [127] and blended it with catechol-functionalized chitosan. Again, immediate in situ gelation was achieved via the thermal transition of the PEO-PPO-PEO. Adhesive characteristics were imparted to the system via the catechol groups on the chitosan, which hydrogen bonded with other catechol groups on the chitosan, the thiols, and components in the tissues. A novel approach was used by Fan et al. [128]. The system they designed consisted of DOPA conjugated gelatin, a rapid cross-linker Fe^{3+}, and genipin. While the dopamine moieties impart interfacial adhesion with surrounding tissue, the Fe^{3+} served as a rapid cross-linker by forming complexes with the catechol groups (**Figure 21**). Because these complexes are unstable due to their reversibility, genipin was included in the formulation. It gradually reacted with the amino groups on the gelatin over hours, providing stable network cohesion over time. Metal-DOPA bonds can reform after breaking, so separated pieces of hydrogel can remerge when placed in contact with one another [129]. Krogsgard et al. [120] took advantage of this property to create "self-healing" DOPA-functionalized gels composed of polyallylamine in solutions of $FeCl_3$. Oscillatory rheology quantitatively shows the spontaneous reformation of separated hydrogel pieces (**Figure 22**).

2.4.2. Gecko-inspired adhesives

Another type of nature-inspired sealant comes from geckos. Geckos have an amazing ability to climb walls because their feet are covered with millions of tiny hairs that provide significant adhesion. Only in the last twenty years or so has the mechanism responsible for this adhesion

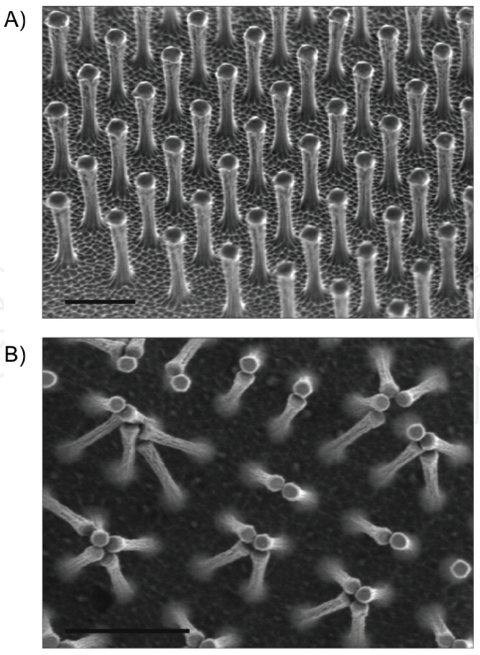

Figure 23. (A) Scanning electron micrographs of polyimide hairs in a gecko-inspired adhesive. (B) Example of bunching pillars, which could reduce adhesive strength of the adhesive (scale bar 2 μm) [134]. Copyright 2003. Reproduced with permission from Nature Publishing Group.

become understood. While any submicron object can stick to a surface, the strength of the adhesion depends on the shape and chemistry involved [130–133]. In the case of hydrophilic materials, capillary action with absorbed water plays a role [132, 133]. In certain sub-micron size ranges, van der Waals forces also promote adhesion to surfaces. The diameter of gecko hairs is such that both capillary action and van der Waals forces are maximized [131], so they can climb surfaces of varying hydrophilicity [134]. To create a gecko-inspired adhesive, one must manufacture a flat surface containing pillars that are sufficiently flexible so they can act in unison to adhere to a substrate (**Figure 23A**). The density of pillars must be maximized in order to generate sufficient adhesion force [134]. Bunching of the pillars (**Figure 23B**) is one mechanism that decreases adhesive strength [134].

Gecko adhesion disappears when submerged in water [135, 136]. An interesting approach to overcoming this limitation and developing a wet/dry adhesive was taken by a group who combined gecko- and mussel-inspired materials into one device. They fabricated pillars from poly(dimethyl siloxane) (PDMS). Separately, they synthesized a mussel mimetic polymer, poly(dopamine-methacrylamide-co-methoxy-acrylate) and used it to coat the PDMS. The addition of the mussel mimetic material to the PDMS increased its wet adhesion by 15 times. However, adhesion was only studied on inorganic surfaces [137]. Mahdavi et al. [138] developed a wet/dry gecko-inspired adhesive and examined adhesion to organic substrates. A micropatterned biodegradable (polyglycerol sebacate acrylate) elastomer was used. It was coated with oxidized dextran to introduce a mechanism for covalent cross-linking with tissue. Simultaneously, the aldehydes reacted with the free hydroxyl groups on the glycerol subunit of the elastomer. Coating the pillars of elastomer with the dextran significantly increased the interfacial adhesion strength in vitro and in vivo.

3. Next-generation applications in tissue engineering

Tissue engineering is a fast-growing area of research that seeks to rebuild damaged tissues and organs. Current strategies involve seeding biomaterials, called scaffolds, with cells and/or biologically active molecules that allow or induce tissue regrowth in a three-dimensional structure [139]. Tissue engineering of certain areas in the body, particularly cartilage [122] and the intervertebral disc [140, 141], is not thought to be clinically feasible without a scaffold that can form an interface with surrounding tissue, eliminating the risk of dislocation and restoring mechanical functionality by adequately transmitting forces to and from the surrounding tissue [122, 140–142]. A scaffold could potentially be sutured in place, but ideally, it would integrate with surrounding tissues via a bioadhesive mechanism while supporting encapsulated cellular function.

Fibrin was the first class of adhesives to be studied for tissue engineering because the gels are completely biocompatible, biodegradable, and capable of delivering growth factors [143, 144]. Additionally, fibrin has been shown to be permissible to in vitro mesenchymal stem cell differentiation toward a chondrogenic lineage [145]. Promising in vivo results with fibrin have been reported in adipose [146], bone [147, 148], cardiac [149], and neural tissue engineering

[150]. Despite these positive results, there are significant limitations with using fibrin adhesives for some tissue engineering applications. Fibrin glues are unstable over time, thus making them non-ideal for the long repair processes [151]. The low mechanical properties make the glues inappropriate for load bearing applications [152, 153], like cartilage and the intervertebral disc. Fibrin gels also have a low cohesive strength with tissue [154, 155].

Besides fibrin glue, the efficacy of other bioadhesive polymers as in situ forming cell carriers for tissue engineering has not been extensively studied. Rather, the biocompatibility of cured adhesives with surrounding cells is typically investigated in the development of new glue formulations. The presence of reactive molecules, such as glutaraldehyde, aldehydes, NHS esters, or the presence of toxic monomers, as in cyanoacrylates, is likely to adversely affect encapsulated cells prior to gel network formation. Only a few groups have sought to investigate this. Adhesive hydrogels composed of gelatin, coupled to oxidized hyaluronic acid (DOO 40%), and cross-linked with adipic acid dihydrazide were characterized as cell carriers. The adipic acid dihydrazide (**Figure 24**) bridged hyaluronic acid-gelatin molecules via an imide bond. Intervertebral disc cells were encapsulated within the gels by suspension in the macromer solution prior to cross-linking. Two days after gel formation, viable cells were shown to be attached to the material [156]. Chondrocytes were shown to survive for 3 weeks after being encapsulated within chondroitin sulfate-NHS networks and combined with bone marrow and recombinant bone morphogenetic protein-2 [157]. These are promising preliminary results, but it is important to note that most current bioadhesive polymers have functional groups that are not only reactive with components of ECM, but cell membranes, as well. More in-depth studies are warranted, as experimental outcomes are likely to be impacted by cell type and density, material reactivity, concentration of reactive groups, and the presence of biomolecular signals such as growth factors.

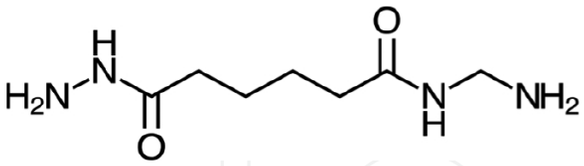

Figure 24. Chemical structure of adipic acid dihydrazide.

Wiltsey et al. [142] investigated the use of polysaccharides without reactive groups as bioadhesive tissue engineering scaffolds. Thermosensitive copolymers of poly(N-isopropylacrylamide) grafted with chondroitin sulfate (PNIPAAm-g-CS) containing mucoadhesive alginate microparticles as the adhesion mediators were developed. Below its lower critical solution temperature (LCST) around 30°C, PNIPAAm-g-CS forms a miscible solution with water. Above the LCST, the PNIPAAm becomes hydrophobic and an elastic hydrogel is formed without the use of monomers or cross-linkers [158]. Alginate microparticles and human embryonic kidney 293 cells were suspended in aqueous solutions of PNIPAAm-g-CS and encapsulated in the polymer network upon gelation at physiological temperature. Inclusion of the alginate microparticles significantly increased the tensile adhesive strength compared with PNIPAAm-g-CS alone and fibrin glue. Also, the formulation exhibited significantly less

cytotoxicity than PNIPAAm-g-CS formulations containing CS-aldehyde as the adhesion mediator. The microparticle-hydrogel composites are now being investigated as scaffolds for intervertebral disc tissue engineering.

4. Conclusions

Due to differences in mechanical properties and cellularity in the various tissues of the body, it would be impractical to develop one sealant that can serve all applications [6]. However, there are some basic requirements that all sealants must have in order to meet present and future clinical needs:

- Easy to apply and rapid solidification to conform to irregular shaped defects or tissue areas.
- Able to provide sufficient mechanical support to the injured tissue as it heals.
- Strong adhesion in order to maintain approximation of tissue pieces, prevent dislocation, and/or ensure adequate transmission of forces across tissue/implant interface.
- Provoke a minimal degree of inflammation or toxicity from surrounding tissues with no risk of disease transmission.
- Biodegradation within a time frame that corresponds to the gradual formation of new tissue.
- Able to promote tissue growth and repair by acting as a suitable 3D culture system by promoting cell adhesion and extracellular matrix production.
- Possible to produce in large scale quantities and cost effective.

Presently, no current bioadhesives have been shown to fulfill all these requirements. Unanswered questions still exist on the suitability of the current formulations for tissue engineering applications. As the field of biomedical sealants evolves to encompass new applications, researchers are working to develop new formulations with increasing biocompatibility, adhesive strength, flexibility and degradability. These advances promise to improve clinical outcomes by enhancing bleeding control and wound healing. In the long term, the use of bioadhesives in tissue regeneration research will become more prominent. New innovations will pave the way towards making orthopedic and musculoskeletal tissue engineering clinically successful in the future.

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Author details

Andrea J Vernengo

Address all correspondence to: Vernengo@rowan.edu

Henry M. Rowan College of Engineering, Rowan University, Glassboro, NJ, USA

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